Genetic Susceptibility to Lead Poisoning

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Major strides have been taken in the regulation of lead intoxication in the general population, but studies using genetic markers of susceptibility to environmental toxicants raise the question of whether genes can make certain individuals more vulnerable to environmental toxins such as lead. At least three polymorphic genes have been identified that potentially can influence the bioaccumulation and toxicokinetics of lead in humans. The first gene to be discussed in this review is the gene coding for δ-aminolevulinic acid dehydratase (ALAD), an enzyme of heme biosynthesis, that exists in two polymorphic forms. The resulting isozymes have been shown to affect the blood and bone lead levels in human populations. The effects of ALAD in lead intoxication have also been studied in laboratory mice that differ in the genetic dose for this enzyme. The second gene reviewed here is the vitamin D receptor (VDR) gene. The VDR is involved in calcium absorption through the gut and into calcium-rich tissues such as bone. Recent findings suggest that VDR polymorphism may influence the accumulation of lead in bone. Finally, the third gene to be discussed here that may influence the absorption of lead is the hemochromatosis gene coding for the HFE protein. The presence of mutations in the HFE gene leads to hemochromatosis in homozygotic individuals. Because of the associations between iron and lead transport, it is possible that polymorphisms in the HFE gene may also influence the absorption of lead, but this has not yet been studied. More studies will be needed to define the role of these genes in lead intoxication. Key words: ALAD, δ-aminolevulinic acid dehydratase, hereditary hemochromatosis, lead accumulation, lead toxicity, polymorphism, vitamin D receptor. — Environ Health Perspect 108(suppl 1):23-28 (2000). http://ehpnet1.niehs.nih.gov/docs/2000/suppl-1/23-28onalaja/abstract.html

Exposure to lead in the environmental and occupational settings continues to be a serious public health problem (1-5). At high exposure levels, lead causes encephalopathy (6,7), kidney damage (8,9), anemia (10), and toxicity to the reproductive system (11,12). Lead exposure may also induce hypertension in some individuals (13,14). Even at lower doses, lead produces alterations in cognitive development in children (15-19). A safe level of lead exposure has not been defined, as health risks associated with lead are found at ever lower doses.

Pinpointing the health risks associated with low-level exposures to lead will have important implications with respect to its regulation. Health-based guidelines limiting occupational and environmental exposures to lead have become more stringent over the past decade and are now thought to protect most of the population against major adverse health effects (20–22). However, genetically susceptible individuals may not be fully protected by current regulatory standards. Better understanding of genetic factors that influence susceptibility to lead-induced intoxication could have significant ramifications for public health and intervention initiatives (23,24).

Researchers have identified a small number of genes that induce susceptibility to environmental toxicants, and much interest has developed in that area. From these strides, scientists at the National Institute of Environmental Health Sciences have conceived the Environmental Genome Project to study environmental susceptibility gene

variants. It is expected that this information will help to identify and protect susceptible individuals from environmental hazards and change public health policy (25).

The three genes to be discussed in this review are the δ-aminolevulinic acid dehydratase (ALAD) gene, the vitamin D receptor (VDR) gene, and the hemochromatosis gene. Polymorphisms of the ALAD gene have been associated with the accumulation and distribution of lead in the blood, bone, and internal organs in humans and animals. The VDR gene has been implicated in the control of calcitriol levels in serum, which normally regulates calcium absorption and can in turn affect lead levels. The hemochromatosis gene, associated with a disease that leads to excessive iron accumulation, may also influence the absorption of lead and will also be briefly discussed.

δ-Aminolevulinic Acid Dehydratase Gene

The hematopoietic system is one of the target organs in lead poisoning. One of the most important mechanisms of lead toxicity is its effect on enzymes in the heme biosynthetic pathway. The enzymes in the biosynthetic pathway of heme in which the effects of lead are of the highest clinical interest are ALAD (porphobilinogen synthase; EC 4.2.1.24) and ferrochelatase, both of which are inhibited by lead (26) (Figure 1). Over 99% of the lead present in blood accumulates in erythrocytes. Of this, over 80% is bound to ALAD (27).

It has been recognized that ALAD, the second enzyme in the heme biosynthetic pathway, plays a role in the pathogenesis of lead poisoning (27). The inhibition of erythrocyte ALAD activity is a sensitive indicator of exposure to lead and has been used as a diagnostic tool (28-30). The series of reactions leading to heme synthesis begins with succinyl coenzyme A (CoA) and glycine and ends with the insertion of an Fe2+ into a molecule of protoporphyrin. In the first step of heme synthesis, the enzyme aminolevulinic acid (ALA) synthase catalyses the formation of ALA from glycine and succinyl CoA within the mitochondrial matrix. Lead does not significantly inhibit ALA synthase, as demonstrated in laboratory mice (31). In the second step of heme synthesis, ALAD catalyzes the formation of porphobilinogen from two molecules of ALA. ALAD is the most sensitive enzyme to lead in the heme pathway and has a high affinity for the metal. Lead binds the enzyme's SH group, which normally binds zinc, preventing the binding of ALA (32). Because of its high sensitivity to inhibition by lead, ALAD activity has been used as a laboratory tool for the detection of lead intoxication. For example, a blood lead concentration of 15 µg/dL results in a 50% inhibition of ALAD activity (33).

Because lead effectively inhibits ALAD activity, resulting in accumulation of ALA in blood and urine, urinary ALA has also been used as a biomarker for lead exposure or a marker of early biologic effect of lead (34). ALAD porphyria is an autosomal recessive disorder resulting from a homozygous deficiency of this enzyme. Because of an almost complete lack of ALAD activity, patients excrete a large amount of ALA into the urine (35). ALA has neurotoxic activity and may contribute to lead-induced toxicity to the brain (36).

Later in the hematopoietic cycle, the enzyme ferrochelatase introduces iron into the protoporphyrin molecule to form heme. Lead

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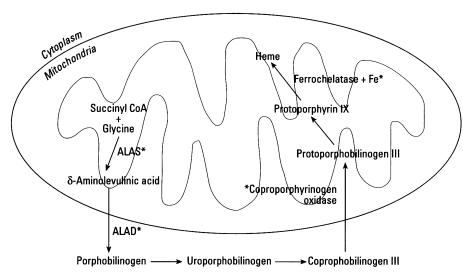


Figure 1. Lead interactions in the heme pathway. ALAS, δ -aminolevulinic acid synthase; CoA, coenzyme A.The heme biosynthesis pathway is represented. Several enzymes in the pathway can be affected by lead; two of the most clinically important are ALAD and ferrochelatase. Both these enzymes are inhibited by lead. Their activity can be measured directly or by the measurement of accumulation of their respective substrates. In the presence of lead, δ -aminolevulinic acid accumulates when ALAD is inhibited. Inhibition of ferrochelatase results in the increased production of zinc protoporphyrin.

inhibits ferrochelatase activity and therefore prevents incorporation of iron into hemoglobin. This reaction also leads to the binding of zinc, producing zinc protoporphyrin (ZPP) (37). The presence of ZPP has been proposed as an indicator of recent lead intoxication and thus can be used as a biomarker of exposure. However, because of the abundance of hemoglobin, even in serious cases of lead intoxication, increased ZPP is relatively harmless because it may constitute less than 1% of the total hemoglobin produced (37).

Human Polymorphism of ALAD and Lead Poisoning

The gene that encodes ALAD exists in two polymorphic forms that may modify lead toxicokinetics and ultimately influence individual susceptibility to lead poisoning. The enzyme is encoded by a single gene located in chromosome 9q34, which has two co-dominant alleles, ALAD1 and ALAD2. It was first discovered to be polymorphic in 1981 by Petrucci and colleagues (38). Later, the cDNA was cloned and the gene sequenced by Wetmur and coworkers ($3\overline{9}$,40). The ALAD₂ allele is the least common form, occurring in 20% of the Caucasian population and more rarely in populations of African and Asian descent (24,38,41). The expression of these alleles results in three distinctly charged forms of the isozymes. These are designated ALAD1-1, 1-2, and 2-2, which can be identified and separated by electrophoresis. The difference between the ALAD2 and the ALAD1 polypeptides is a substitution of asparagine for lysine at residue 59, resulting from a single nucleotide change in position 177 of the coding region (24). It appears that

this substitution changes the electrical charge of the molecule resulting in ALAD2 having a higher affinity for lead than ALAD1.

Given the ALAD polymorphism found in humans and the knowledge that the enzyme is sensitive to inhibition by lead, it was reasonable to believe that this polymorphism could lead to differences in susceptibility to lead among the human population. A small study of 202 workers occupationally exposed to lead showed that individuals who carried one or two copies of the ALAD2 allele presented higher blood lead levels than individuals with only the ALAD1 form of the gene (42). To further investigate this, Astrin and colleagues determined the ALAD genotype in over 1,000 blood samples submitted to the New York City Lead Screening Program (33). They found that a higher than expected proportion of lead-exposed individuals were either homozygous or heterozygous for the ALAD₂ allele. Furthermore, the presence of the ALAD2 allele was associated with a 4-fold increase in the ability to retain lead in the blood at levels above 30 µg/dL. In comparison, only 8% of individuals with blood lead levels below 30 µg/dL carried the ALAD₂ allele. This finding supported the notion that the presence of the ALAD2 allele increases blood lead levels in exposed individuals. In a follow-up study, 202 male workers in a German factory occupationally exposed to lead and a group of 1,278 environmentally exposed children were assessed for ALAD genotype and blood lead levels (43). Individuals in both groups who carried one or two copies of the ALAD2 allele had blood lead levels 9-11 µg/dL higher than individuals who were homozygous for ALAD₁. This was

a significant finding and was the first to show a strong association between ALAD polymorphisms and blood lead levels in a large cohort.

Other investigations have challenged some of these findings. Smith and colleagues conducted a study of over 600 carpenters exposed to low levels of lead (below 10 µg/dL). In contrast to the studies summarized above, these investigators did not find that individuals with the ALAD₂ allele have significantly different blood or bone lead levels than those with the ALAD₁ allele (44). These researchers argued that the effect of the ALAD allele variants may only come into play when other lead-binding sites have been saturated. Therefore, the contribution of ALAD variants in the resulting bioaccumulation would only be observable at high exposure levels (45). It was later proposed by these investigators that hemoglobin A1 may be an important lead-binding protein that could significantly influence the bioaccumulation of lead (46). A study of lead-binding proteins revealed that ALAD had the strongest affinity for lead, whereas no lead was found bound to hemoglobin (27,47). It appears that the evidence is strongest in suggesting that ALAD is the most important lead-binding protein in blood. Furthermore, studies of lead protein binding showed that 84% of proteinbound lead was bound to ALAD in ALAD₂ carriers, while 81% was bound to this enzyme in the ALAD1 homozygotes (27). These data also suggest that although both forms of the enzyme bind great quantities of lead, ALAD2 may bind the metal with the highest affinity.

Evidence is mounting to suggest that ALAD plays an important role in the bioaccumulation of lead. Exactly how ALAD, and ALAD polymorphism in particular, influences the distribution of lead to other target organs is still a question open for research. Two different scenarios may be proposed. In the first, increased binding of lead to ALAD, especially to ALAD2, could result in increased distribution of lead to other target organs such as kidney and brain. Conversely, it is possible that ALAD could serve as a sink, keeping lead sequestered in the blood. ALAD2 could serve as a high-affinity substrate, retaining lead in the blood and therefore protecting other organs. In this case, people who have the ALAD2 allele could experience less severe effects of lead on kidney and brain and lesser accumulation of lead in bone while at the same time having higher blood lead levels than ALAD₁ homozygotes exposed to the same doses of lead.

To investigate the above scenarios, some markers of the effects of lead have been studied in human populations and their relation to ALAD genotype interpreted. To determine whether ALAD polymorphism can influence lead excretion, Schwartz and co-workers (48) studied a group of Korean lead battery manufacturing workers with a mean blood lead

concentration of 25 µg/dL. Workers were given oral doses of dimercaptosuccinic acid (DMSA), a chelating agent used to treat lead intoxication. The results showed that subjects heterozygous for ALAD excreted less lead through the urine in response to the DMSA treatment than did the ALAD1 homozygotes (48). It may be possible that the presence of ALAD2 increases the retention of lead in blood and decreases the amount of chelatable lead. Treatment with DMSA, therefore, would not be as effective in ALAD2 carriers. Other investigators found that ALAD genotype may influence kidney function, which may also affect excretion of lead (49). In workers exposed to low levels of lead, subclinical kidney effects were more prominent in heterozygous individuals compared to ALAD1 homozygotes (44). The evidence summarized above suggests that the ALAD2 phenotype may enhance the detrimental effect on lead toxicity by affecting kidney function and decreasing the amounts of lead that are excreted after chelation.

Other studies suggest a more complex role for ALAD polymorphism in the toxicity of lead and support the possibility that ALAD2 may be protective. For example, in a study of 65 lead-exposed workers with a mean blood lead level of 27.9 µg/dL, the presence of ALA in plasma was about 30% higher in the ALAD1-1 subjects than in the ALAD1-2 heterozygous individuals (36). This is significant, since it has been argued that the neurologic effects of lead are due, at least in part, to the neurotoxicity of ALA (50). These results are in concordance with another study in a small number of lead-exposed adolescents with the ALAD1-2 phenotype. That investigation showed that ALAD2 carriers performed better in neuropsychologic tests of attention than ALAD₁ homozygotes exposed to the same levels of lead (51). These data suggest that ALAD2 may serve some protective role in lead-induced neurotoxicity. It is not known from these results how ALAD polymorphism may influence the transport of lead to the target organs, particularly the brain. This is important, since lead may also be directly toxic to neurons (52). It may be that ALAD2 plays a protective role by keeping lead bound in the blood compartment. Supporting this notion is the finding that ALAD1-1 subjects transfer more lead into bone even when ALAD2 carriers have higher blood lead levels (53). In addition, higher ZPP levels can be detected in ALAD1-1 individuals compared to heterozygous (54). Taken together, these data begin to suggest that even though ALAD2 carriers accumulate higher blood lead levels, it is ALAD1-1 homozygotes who may experience more severe effects of lead in brain, bone, and hemopoiesis, as evidenced by ZPP levels. In any case, it appears clear that the effects of ALAD polymorphism on lead toxicity are multifaceted and complex. More research will be needed to elucidate this issue.

ALAD Polymorphism in Laboratory Animals

Animal models of variants in the ALAD gene may help in defining the role of the enzyme in lead toxicity. It has been discovered that two common laboratory strains of mice differ in their expression of the ALAD gene. Investigators had already shown that hepatic ALAD enzyme activity was higher in DBA/2 mice than in the C57BL/6 strain (55,56). Later it was shown that DBA/2 mice have two times the dose of ALAD, due to a duplication of the gene. In comparison, C57BL/6 mice have only one copy of the gene and therefore only one dose of the enzyme (57). This duplication of the ALAD gene in DBA/2 mice explained the higher levels of enzymatic activity in these animals. Further, hybrid animals $(C57BL/6 \times DBA/2)$ were found to have intermediate levels of enzyme activity (57).

We have capitalized on this genetic difference in the mouse strains to study the role of ALAD in the accumulation and distribution of lead. To that end, we exposed DBA/2 and C57BL/6 mice to the same acute doses of lead in the drinking water (23). For instance, adult mice were exposed to 500 ppm lead acetate in the drinking water for 14 days and blood lead levels were determined. The animals were perfused in order to extract the lead-containing blood from the internal organs. Then kidneys, liver, and brain were extracted and assessed for lead content. We found that the DBA/2 mice, which have a duplication of the ALAD gene, accumulated twice the amounts of lead in

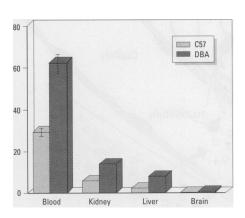


Figure 2. Bioaccumulation of lead in mice that differ in the gene dose for ALAD. DBA/2 mice have two copies of the ALAD allele, whereas C57BL/6 animals have a single copy of the gene. Mice were given 500 ppm lead acetate in the drinking water for 2 weeks. The DBA animals accumulated twice the amounts of lead in the blood, kidney, and brain and 4 times the levels of lead in liver than the C57 animals exposed to the same doses. Values are given as micrograms per deciliter for blood and micrograms per gram of tissue for the organs.

blood than C57BL/6 mice (Figure 2). The DBA animals also accumulated an average of 2.4 times higher lead concentrations in the kidneys, 4.1 times the lead in the liver, and 2.5 times the levels in brain as the C57 mice exposed to the same doses. In other experiments we showed that hybrid mice presented intermediate levels of lead in the blood and target organs when exposed to the same levels as the purebred animals (23).

Interestingly, ZPP levels increased with increasing lead exposure in C57 mice, suggesting that the hematopoietic system of these mice was highly sensitive and affected by lead exposure even when these animals retained relatively low levels of lead in the blood (Figure 3). This may be due to the lower amounts of ALAD in the blood of these animals, which would allow for lead unbound to ALAD to affect the production of ZPP. In contrast, in the DBA mice the situation is reversed. The higher concentration of ALAD in the blood provides a high-affinity substrate for lead, reducing its effect on the production of ZPP. These findings compare well to the observations made in humans (54) and may suggest that these mouse strains can be used as a model for studying the role of ALAD in lead toxicity. However, it must be noted that the genetic difference in these mice is due to a duplication of the gene rather than a polymorphic form as seen in humans. Developing transgenic mice with the ALAD₂ gene may be a more accurate model of the human system.

It appears from these results that the presence of more ALAD in the blood facilitates the binding of lead by increasing the substrate

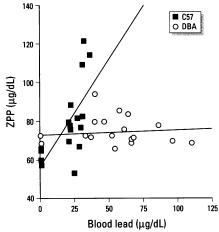


Figure 3. Blood lead levels plotted against ZPP levels in DBA and C57 mice. Animals were given doses of 0, 250, 500, and 1000 ppm of lead in the drinking water for 14 days (4 animals in each dose group). ZPP levels in DBA animals remained constant even when blood lead levels increased to over 100 μ g/dL. In contrast, ZPP increased sharply with increasing lead dose, while blood lead levels remained relatively low in C57 mice. Data adapted from Claudio et al. (*23*).

to which the metal can bind. This is consistent with the estimations of high proportions of lead in blood bound to ALAD (27,58). This increased binding of lead to ALAD may then facilitate the distribution of lead to other target organs in the DBA/2 animals.

Although this mouse model differs from the human situation in that it involves a gene duplication rather than a mutation, we have used it to study the role of ALAD in leadinduced toxicity. Our findings suggest that ALAD plays an important role in the bioaccumulation of lead in tissues and therefore may play a pivotal role in lead's toxicokinetics. Both in animals and in humans, ALAD, together with lead exposure level appears to be a factor in the accumulation and distribution of lead, which in turn affects the pathologic effects that will be exerted by the metal. The rapid and accurate determination of the ALAD genotype permits the screening of populations to identify individuals who are genetically susceptible to higher blood lead levels (30,58). Further research is needed to understand the role of this enzyme in lead toxicity in order to develop any screening strategies for risk assessment in populations of individuals exposed to lead.

Polymorphism in the Vitamin D Receptor Gene and Lead Intoxication

The Role of Vitamin D in Mineral Transport

Sunlight produces the activation of vitamin D in the skin to 1α25(OH)₂D₃ (calcitriol), the blood-borne hormonal form of vitamin D that is involved in mineral absorption. The role of vitamin D in calcium and lead absorption is illustrated in Figure 4. The vitamin D hormone circulating in the blood can then bind to VDRs in the nucleus of intestinal cells as well as in kidney and bone (26). There, the high-affinity VDR appears to activate genes that encode calcium-binding proteins such as calbindin-D, which is involved in intestinal calcium transport (59). Increases in the production of calbindin-D in the intestinal cells result in increased absorption of calcium through the gut.

Because of their similar biochemical nature as divalent cations, calcium and lead often interact in the same biologic systems. For that reason, many of the cellular effects of lead are thought to be due to its effects on the normal function of calcium-dependent systems (60).

Calcium—A O O Mucosal cell

Nucleus

Protein

DNA

D3

receptor

Capillary

10, 25(0H)₂D₃

Bone

Figure 4. Possible role of the vitamin D receptor in the absorption of calcium and lead. The blood-borne form of vitamin D $(1\alpha1,25(0H)_2D_3)$ activates the vitamin D receptor (D3), increasing the production of calcium-binding proteins. These proteins increase the dietary absorption of calcium in intestinal cells. It is possible that this mechanism may also influence the absorption of lead into blood and bone. Data adapted from Devlin (26).

Lead and calcium also modify each other's absorption. For example, dietary calcium deficiency contributes to increased intestinal lead absorption and retention (61-63). In addition, calbindin-D binds lead with high affinity and may be implicated in its transport (64). These data suggest that calcium and lead are cotransported through the gut into the blood, and from there the two metals may be codistributed to calcium-rich tissues such as the bone (65). Through this mechanism it is possible to explain why there is increased lead absorption during dietary calcium deficiency. Calcium deficiency increases the production of vitamin D hormone and therefore the synthesis of calcium-binding proteins. In the presence of lead, proteins such as calbindin-D will bind this metal, increasing its transport (66). In addition, intoxication with lead can produce decreased serum calcitriol, suggesting that lead impairs hormonal synthesis in the kidney (67). In this way lead may also interfere with calcium absorption (68). Together, these data show that the interactions between lead, calcium, and calcitriol are complex and induce modifications of mineral and vitamin levels.

Role of Vitamin D Receptor Polymorphism in Lead Intoxication

The cellular actions of hormonal vitamin D depend on its interaction with the nuclear VDR that regulates the production of calcium-binding proteins. These, in turn, may function in the mineralization and resorption of bone. The VDR exists in several polymorphic forms in humans (69). This polymorphism of common allelic variants can be used to predict differences in bone density and it is said to account for up to 75% of the total genetic effect on bone density, as first determined in a study of healthy monozygotic and dizygotic twins (70). However, some debate persists on this issue (71). For example, a study of VDR alleles in prepubertal girls showed that genotype had an effect on growth rather than bone density (72). Nevertheless, it is possible that the effect of VDR on bone density is more detectable with age.

At least three genotypes of the VDR gene have been identified. These are defined by the restriction fragment length polymorphisms (RFLPs) resulting from cutting the DNA with three different restriction enzymes, Taq I (73), Fok I (74), and the most widely studied, BsmI (75). These RFLPs have been correlated with bone mineral density and circulating levels of osteocalcin (69,76,77).

The polymorphism defined by the restriction enzyme BsmI results in three genotypes denoted bb when the restriction site is present, BB when it is absent, and Bb when the two alleles are present. The BB genotype has been associated with lower bone mineral densities, particularly in women (71,75,78)

and may play a role in the development of osteoporosis and rheumatoid arthritis (73). Women expressing the BB genotype may have 2–10% lower bone mineral densities than those with the bb form of the gene (79). Similarly, mineral bone densities have been found to be 7% lower in men homozygotic for BB compared with bb or heterozygous (80).

Because of these polymorphisms and their effect on bone mineralization, it can be expected that these genetic variants may also influence lead accumulation in bone. Lead accumulates in bone at different rates through the life cycle, showing lower rates of deposition in the earlier years and increasing in middle-aged and elderly subjects (81,82). The first study to address the role of VDR genotype on bone lead accumulation has been conducted. Using X-ray fluorescence to determine the levels of lead in bone in a group of leadexposed workers, investigators found that bone lead content is higher in individuals with the BB genotype, intermediate in heterozygous and lower in bb homozygous (83). These observations suggest that VDR polymorphism may not only affect bone mineral density but may also influence the accumulation of lead in bone. Further investigation on the role of VDR will be necessary, but the evidence suggests that it may play a role in susceptibility to lead bioaccumulation. The results of this study show that the influence of VDR on accumulation of lead in bone was too high in BB individuals to be explained by bone mineral alone. It will be interesting to see how this polymorphism may affect bone lead levels in other populations.

Possible Role of the Hemochromatosis Gene in Lead Intoxication

Hemochromatosis is a disease in which excessive quantities of iron are deposited in many internal organs, particularly the liver, leading to progressive tissue damage. The disease has been estimated to occur in 1 out of every 300 Caucasians (84), although genotyping studies estimated that the incidence may be 1 in 200 (85). The disease state appears most commonly at the ages of 30–40 years and is treated by periodic extraction of blood from the patient, thus reducing the iron overload. Iron chelation may also be recommended.

A gene localized in chromosome 6p21.3 has been identified to code for a defective protein involved in hemochromatosis. The gene corresponds to the major histocompatibility Class I-like family and codes for a protein designated HFE (86). Two missense mutations in this gene have been identified that lead to hemochromatosis in homozygotic patients; the most common of these mutations is designated C282Y. The mutations are present in over 80% of patients with the disease (87). In a study conducted in New Zealand, 38% of the

general population is heterozygous for either one of the mutations (85).

An important association has been made between iron deficiency and increased lead absorption and toxicity (88). For example, a study conducted in two-year-old children showed that iron-deficient children did not recover as well from lead intoxication after undergoing chelation therapy and failed to achieve developmental landmarks compared with children also exposed to lead but who had normal levels of iron (89). This is compelling data that point to the strong influence of iron status not only in the accumulation of lead but also in its toxicity. Ironically, hemochromatosis patients may be at risk of increased lead absorption as if they were iron deficient. It has been found that homozygous individuals who have the disease accumulate more lead than do those who do not have the gene. Heterozygous individuals had intermediate blood lead levels (90). This is strong evidence to suggest that the hemochromatosis gene may induce susceptibility to increased lead absorption.

At least two mechanisms for the increased absorption of lead in hemochromatosis gene carriers can be postulated. Since the discovery of the HFE gene in hemochromatosis patients, much has been learned about its function in iron homeostasis. It appears that HFE binds to the transferrin receptor, reducing its ability to bind to transferrin and thus decreasing the absorption of iron in the gut in normal individuals (87,91). Hemochromatosis patients lack a functional HFE protein due to mutations in the gene. This lack of HFE increases the expression of transferrin receptors in the intestine and absorption of iron increases as if the patient were iron deficient (92).

Another mechanism for the role of HFE mutations in the development of hemochromatosis may also be involved. It was found recently that knockout mice that lack the gene for HFE have increased expression of the divalent metal transporter (DMT-1) protein in the duodenum. These mice show an increase in mRNA for DMT of over 7-fold (93). Support for the role of DMT comes also from studies in humans. Biopsies of the duodenum of hereditary hemochromatosis patients revealed a 3-fold increase in mRNA levels above those found in biopsies of control patients (94). These findings suggest that the HFE protein may influence the expression of other metal transporters such as DMT in the gut and modify the absorption of other metals in addition to iron. The findings also raise the question of whether carriers of the HFE mutations may also induce differential absorption of metals. For example, individuals heterozygous for either of the HFE mutations show increased serum iron and transferrin saturation levels (85). Given that these mutations are relatively common, occurring in over one-third of the Caucasian population, it may be interesting to determine how these mutations may influence absorption to other metals. Information on the hemochromatosis gene is very new, since the HFE gene was discovered only 3 years ago. Studies on how this gene may influence lead absorption have not been reported.

In conclusion, the influence of genes on lead intoxication is still being defined. The most well-known gene in this regard is the ALAD gene, which has been highly studied in human populations and animal models. This genetic polymorphism appears to have a strong influence on lead absorption and bioaccumulation, but its role in affecting neurotoxicity of lead is still unclear. The roles of the VDR polymorphisms and the HFE gene are even less clear. Both are involved in the transport and bioaccumulation of other divalent cations through the intestinal tract, and for that reason may also influence the absorption of lead. More studies will be needed to define their roles. However, it is clear that more genetic determinants will be discovered to be associated with susceptibility to lead intoxication and to other environmentally induced ailments.

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